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Integrative Modalities that Potentially Benefit Healing

Ronald Glick, MD
Khara Lucius, ND, FABNO
Center for Integrative Medicine at UPMC Shadyside

Disclosures—Dr's Glick & Lucius have no conflicts or disclosures

Ronald Glick, MD

- Medical Director-–Center for Integrative Medicine at UPMC
- Associate Professor of Psychiatry and Physical Medicine & Rehabilitation—University of Pittsburgh School of Medicine

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What we'll cover

- I will focus on complementary/integrative approaches, such as acupuncture & mind-body therapies
- Dr. Lucius will look at nutrition with a specific eye on supplements that may help for wound healing

Integrative Medicine—Definition

Reaffirms the importance of the relationship between practitioner and patient,

focuses on the whole person,

is informed by evidence,

and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines

to achieve optimal health and healing.

Center for Integrative Medicine

20 clinicians of various specialties:

- Acupuncture
- Massage therapy & bodywork
- Chiropractic
- Naturopathic medicine & nutrition
- Biofeedback

Mindfulness Meditation classes

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Why do people use complementary/integrative health?

They're experiencing:

- Chronic health conditions
- Standard biomedical treatments have only gone so far
- Condition is disabling or painful

Wound healing—Potential Targets for Tx

- Inflammation/Inflammatory markers
- Sympathetic/Parasympathetic balance
- Growth factors
- Angiogenesis

Considerations for Tx

- Traditional Chinese Medicine Herbals-taken orally
- TCM herbals-used topically
- Acupuncture
- Moxibustion
- Mind-Body approaches

Acupuncture for Wound Healing—Evidence

- For other areas, there are a # of studies in the west (migraines, back pain, OA, hypertension)
- Paucity of research for wound healing
- Human research is primarily cases or case series
- Animal research is focused on mechanisms, small # of studies
- Limitation many Chinese articles may not come up in standard searches

Traditional Chinese Medicine (TCM)

- Based on Taoist philosophy
- Understanding of health & disease reflective of balance of energy & energy flow through the various organs of the body
- Diagnosis based on constitutional factors & exam (tongue & pulse)
- Treatment focused on diet, herbals, acupuncture, mind-body approaches, movement of energy through the body

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Moxibustion

- Burning of an herb (mugwort) at specific acupuncture points
- Famous in the States, use of Moxa for breech presentation
- Studies appear favorable (1^0 articles in Chinese)
- Meta-analysis underway
- Presumed mechanism peripheral vasodilatation

TCM Herbals—Oral

- Purist use of herbals is to treat a specific imbalance—eg Kidney Qi deficiency
- For treatment of western medicine diagnoses, they may start with what imbalance is likely common, but focus pragmatics
- A # of different individual herbals or combination agents have been studied, with positive findings
- Studies over last decade have focused on mechanism

TCM Herbals—Topical

- 2 Impressive studies both multicenter RCT's with high quality design
- Zhang-agent is Shengji Yuhong ointment
- Li-agent is Moist Exposed Burn Ointment (MEBO)

Zhang, J., et al. (2019). "The Treatment of Low Leg Nonischemic Ulcers With a Traditional Chinese-Pharmaceutical Medium: A Randomized Controlled Multicenter Clinical Study." International Journal of Lower Extremity Wounds **18**(2): 186-191.

Li, W., et al. (2017). "Moist exposed burn ointment for treating pressure ulcers: A multicenter randomized controlled trial." Medicine **96**(29): e7582.

TCM Herbal Ointment-Zhang

- N=400 patients with nonhealing leg ulcers
- Subjects randomized to active agent vs. vaseline gauze x 1 month
- TCM studies commonly separate responders into 4 categories: cured, marked improvement, improved, & unchanged or worse
- They report 1st 3 categories as effective—Tx 99%, control 71%
- If you look at 1st 2 categories—Tx 149, control 51
- Wound reduction %--Tx 81.4, Control 29.7

TCM Herbal Ointment-Li

- N=72 patients with pressure ulcers
- Subjects randomized to MEBO applied daily vs. Placebo x 2 months
- Complete healing–Tx 50 %, control 16.7%
- Wound surface area reduction (cm^2)—Tx 14.6, control 8.7

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Mind-Body Approaches—What's the problem?

- We're stressed
- We're pulled in multiple directions at the same time
- The things we used to do to help aren't available
  - Not enough time
  - Too many demands
  - Physical decline affecting activity tolerance
- We experience a vicious circle between stress, health issues, pain, sleep problems

How do you manage stress?

- Surprisingly, we get a lot of positive responses

  Garden, read a good book, prayer, talk with friends
- We get a lot of “I used to”

  Do yoga, walk, run
- We try to help our patients find some activity that they can incorporate into their daily routine
- Strong evidence on benefits for mood, anxiety, sleep, pain, well-being, stress, general health, quality of life

How does stress vs. mind-body practice affect blood flow?

- Sympathetic tone
  - Elicits fight or flight
  - You need your blood to act
- Parasympathetic tone
  - Rest & digest
  - Facilitates peripheral vasodilatation

What are the common mind-body modalities?

- Yoga
- Tai Chi
- Qi Gong
- Meditation
- Mindfulness practice
- Breathing techniques
- Religious contemplation

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So does mind-body practice increase wound healing?

- Short answer-We don’t know
- Paucity of studies
- Handful of studies of hypnosis or biofeedback
- My feeling is that any effect is largely related to the shift from sympathetic to parasympathetic predominance
- Benefit should be comparable across mind-body approaches

Biofeedback for non-healing foot ulcers

- RCT N=32 subjects randomized to thermal biofeedback vs. Usual Care
- Wound healing—Tx 14/16, control 7/16

Rice, B., et al. (2001). "Effect of biofeedback-assisted relaxation training on foot ulcer healing." Journal of the American Podiatric Medical Association **91**(3): 132-141.

Conclusions

- Evidence is limited for complementary therapies
- Best evidence is for TCM herbal ointments
- No conclusions RE acupuncture or mind-body therapies

  It may be that there's a lack of studies, not studies showing lack of efficacy
- We may consider complementary/integrative approaches for general wellness and support

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Wound Healing: Integrative Support Using Targeted Nutrients

Khara Lucius, ND, FABNO, CNS

UPMC Center for Integrative Medicine

Shadyside Place

Overview

- Wound healing and nutrition
- Omega 3 fatty acids
- Vitamins A, C, and E
- Zinc
- Bromelain
- Curcumin

Wound Healing and Nutrition

- Nutrition status overall -> strong impact on wound healing
- Both macro-and micronutrient status are important
- Micronutrients, arginine, glutamine, vits A, B, C, and D, zinc and iron are essential for inflammatory process and collagen synthesis.
- Both protein-energy malnutrition, and specific micronutrient deficiencies, may contribute
- Double burden of malnutrition (coexistence of overweight/obesity with undernutrition)

Wound Healing and Energy Intake

- Adequate carb necessary for fibroblast production, for migration during proliferative phase, and for leukocyte activity.
- Carbs and fats provide energy to meet intake needs
- Protein and energy requirements of chronic wound pts may increase by 250% and 50%, respectively. (Breslow et al 1993)

Wound Healing and Protein

- Adequate protein intake is necessary to maintain positive nitrogen balance. Goal is to ensure that more nitrogen is ingested in the form of protein, than is being excreted/utilized
- In the proliferative and remodeling phases, protein-energy deficiency may decrease fibroblast activity, delaying angiogenesis and reducing collagen formation

Wound Healing and Protein

- Protein deficiency may be related to inadequate intake OR to wound itself.
- Response to injury may increase metabolic needs of the wound area
- Large amounts of protein can be continually lost through wound exudates.

Protein needs in wound healing

- Stechmiller 2010:
- 1.25 and 1.5 g/kg/d for individuals with chronic wounds
- For those who are severely catabolic, with more than 1 wound, or with a stage III or IV pressure ulcer, requirements may range from 1.5 to 2 g/kg/d p
- Intake at 2 g/kg/d may contribute to dehydration in older adults and individuals with renal insufficiency and should be monitored.

Impact of Malnutrition

- Per USDA data, >12% of American households were food insecure in 2016
- Per Nutritional Screening Initiative (NSI):
- 40% to 60% of hospitalized older adults either malnourished or at risk for malnutrition
- 20% to 60% of home care pts malnourished
- Malnutrition affects up to 85% of nursing home residents at some point during stay.

Co-morbidities

- Even in a state of adequacy-> how do GI concerns impact nutrition status?
- Yildirim et al 2018: 29% of hospitalized pts with T2DM either had malnutrition or had increased risk of malnutrition, with 72% of subjects being overweight or obese.
- Lodebo et al 2018; Carrero et al 2018: Protein-energy malnutrition present in 20–40% of pts w/ stage 4–5 CKD and in 28-54% of pts on dialysis

Targeted Nutrients

Omega 3 Fatty Acids

- O3FAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).
  - ALA – plant sources- nuts, seeds, nut and seed oils
  - DHA and EPA - fish and seafood
- ALA is considered an essential fatty acid as it cannot be synthesized de novo in humans
- ALA may be converted into EPA and DHA, but conversion is unreliable and limited
  - Conversion approx 6% for EPA and 3.8% for DHA (Gerster 1998)
  - Relatively low rate of ALA conversion to EPA/DHA suggests these omega-3 PUFA may be considered conditionally essential.

Role of O3FA

- Many important roles. Most pertinent to wound healing:
  - Cell membrane structure and function
  - Gene expression regulation- via interaction with transcription factors; indirect effects on membrane lipid composition and cell signaling pathways.
  - Antioxidant effect may counteract the oxidative stress of chronic wound state
  - Impacts innate and adaptive immune function

O3FA- anti-inflammatory effects

- Omega-6 and O3FAs can both be used to synthesize SPMs (pro-resolving mediators), local mediators of the resolution phase of inflammation. SPMs may switch off the inflammatory response. (Bannenberg and Serhan 2010)
- Reduction of prostaglandin and COX2 expression in a variety of disease states. (White et al 2019, Trebble et al 2003, Aronson et al 2001, Abdolahi et al 2019)

O3FAs- what is the evidence?

- Fish oil as stand-alone intervention- mixed animal studies; 2 clinical trials
- Also used as component of postoperative enteral immunonutrition formulas also containing arginine and glutamine

Animal models- fish oil

- Topical appl of purified omega 3/6/9 FAs fatty acids for surgically induced wound closure in mice. Topical oleic acid accelerates wound closure; ALA delayed. (Cardoso et al 2004)
- Rats fed O3FA as part of the diet compared to those fed omega 6-> weakened mechanical properties at the site of wound repair (Albina et al 1993)
- Porras-Reyes et al (1992) found that both EFA deficient and EFA replete rats had same course of histological and immunological changes in response to wounding, suggesting EFA status did not influence wound healing in rats.

Placebo-controlled clinical trials- fish oil

- McDaniel et al 2008: 30 healthy volunteers (ages 18-45) received either placebo or fish oil (1.6 g EPA, 1.1 g DHA) QD x 28 days.
  - Decreased plasma AA:EPA from baseline; significantly higher production of proinflammatory cytokine IL-1β at blister wound site at 24 hours (increased expression of proinflammatory cytokines within few hours post tissue injury shown to correspond to inflammatory stage of wound healing/normal repair. Diminished production of proinflammatory cytokines in initial stage of wound healing may be associated with impaired wound healing)

Placebo-controlled clinical trials- fish oil

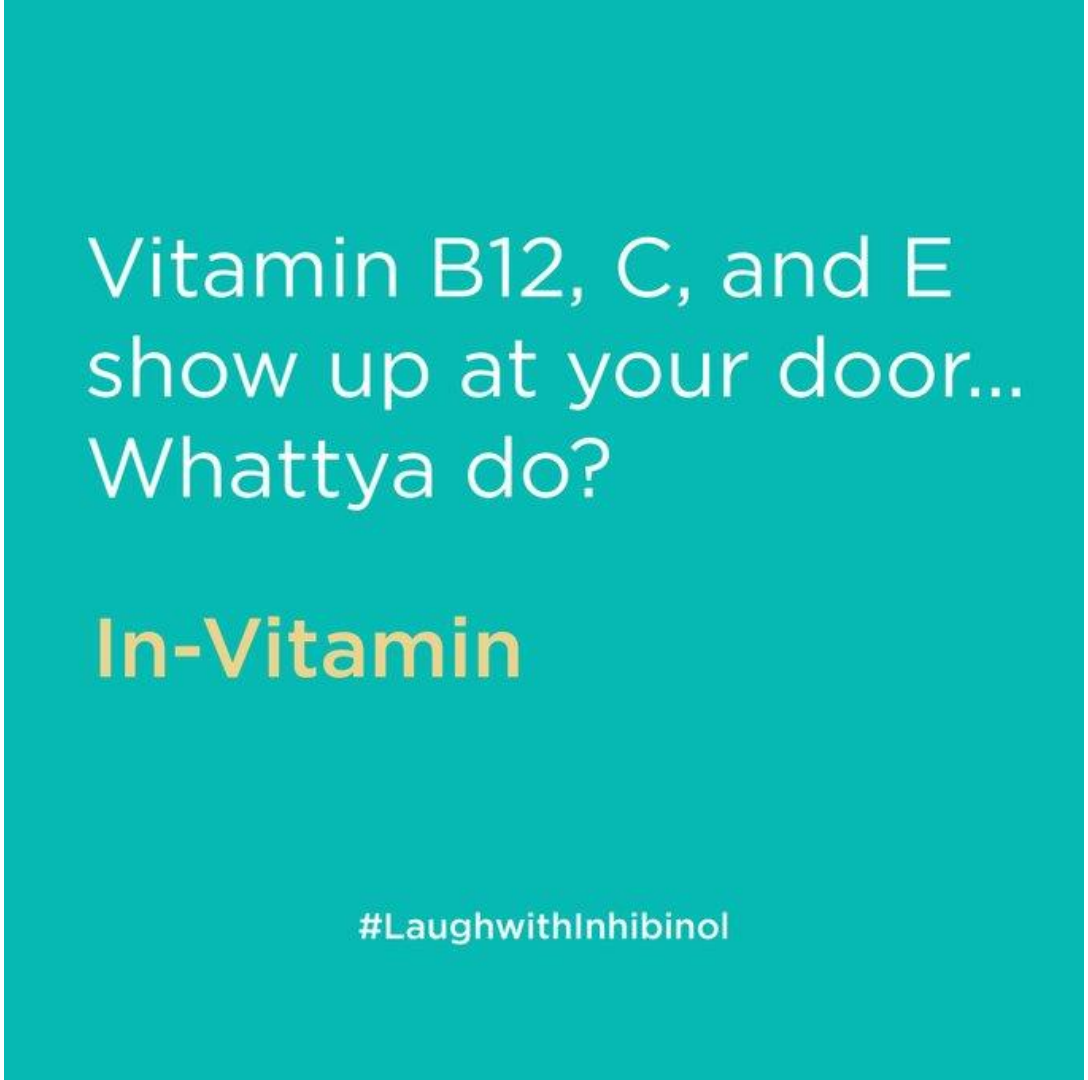
- McDaniel et al 2011: 18 healthy volunteers (ages 18-45) received placebo or fish oil (1.6 g EPA, 1.2 g DHA) QD x 28 days; both groups also took ASA 81mg QD.
  - Significantly lower wound fluid levels of lipid mediators(9-hydroxyoctadecadienoic acid and 15-hydroxyeicosatrienoic acid) at 24 hrs postwounding. Lower levels of myeloperoxidase, a leukocyte marker, at 12 hours. Significantly greater re-epithelialization on Day 5 postwounding.

Immunonutrition with O3FA

- Sittitrai et al 2021: RCT in 116 pts with H&N cancer undergoing surgery. Received either immunonutrition with arginine, glutamine, and O3FA, or standard blenderized diet for 7 days preop & 14 days postop.
  - Significant reduction in mucocutaneous fistula and length of hospital stay; improved nutritional status, including body weight, prealbumin, and transferrin levels.
- Farreras et al 2005: RCT in 66 pts with gastric cancer. Received either postop immunonutrition (supplemented with arginine, O3FA and RNA) or isocaloric-isonitrogenous control.
  - Signficantly higher local hydroxyproline levels; significantly lower wound healing complications with immunonutrition.

Vitamins A, C, and E

- Vitamin A- a primary nutrient involved in the wound healing process; stimulates epithelialization and collagen deposition by fibroblasts; decreased levels of vit A, retinol binding protein, retinyl esters, and beta-carotene noted after burns, fractures and elective surgery
- Vitamin C- suboptimal vit C status shown to impair wound healing and increase risk of wound infection; deficiency associated with increased bleeding in surgical pts. Vit C involved in collagen synthesis, neutrophil function, and complement activity.
- Vitamin E- free radical scavengers such as vitamin E play a role in protecting cellular membrane integrity; chronic wound status can deplete free radical scavengers such as vitamin E



Vitamin C and dental extraction

- Yingcharoenthana et al 2021 randomized clinical trial in 30 subjects undergoing bilateral premolar extraction
- Vit C dosed 600mg QD as PO or slow oral dissolution (local).
- Compared to control, local and oral Vit C resulted in significantly improved soft tissue healing (assessed by socket depth reduction) at 21 days post extraction.

Vitamin C and dental implant surgery

- Li et al 2018: 128 people receiving dental implants were divided into control or Vit C (dosed at 300mg QD x 7 days)
- No difference in pain scores, but subjects who took Vit C had significantly higher healing indices than the controls at day 7 post procedure.

Vit A and E in photorefractive keratectomy

- Vetrugno et al 2001 RDBPCT: 40 pts undergoing PRK (laser surgery) received either placebo, or 25,000 IU retinol palmitate & 230 mg alpha tocopheryl nicotinate for 3 months postop.
  - Time to re-epithelialization significantly faster in vitamin group; haze incidence was significantly reduced; effect stronger for high myopic corrections. High myopic correction group also had significantly better uncorrected visual acuity.

Pressure ulcer prevention in critically ill pts

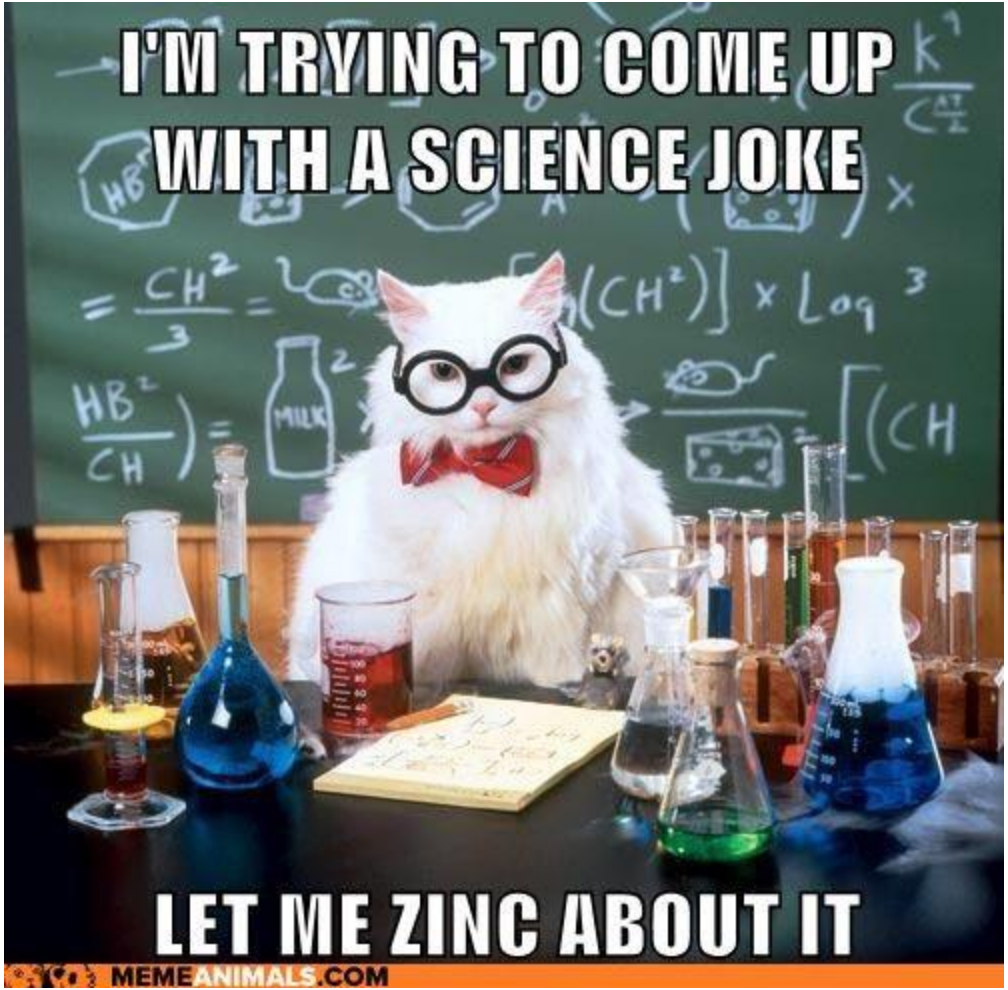
- Theilla et al 2007: Prospective RCT in 100 critically ill people with acute lung injury.
- Enriched diet (with EPA, essential O6FA GLA, and vitamins A 5mg/L, C 844mg/L and E 317 IU/L) was compared with a diet similar in macronutrient composition but without added nutrients.
- A significantly lower rate of occurrence of new pressure ulcers was seen in the intervention group compared to the control group

Pressure ulcer prevention in critically ill pts

- Theilla et al continued
- Day 4: 23 of 49 pts had pressure ulcer in the control group; 12 of 46 in intervention group
- Day 7: 24 of 49 pts had pressure ulcer in control group; 15 of 46 in intervention group

Zinc

- Membrane repair
- Zinc crucial for skin health; required for normal keratinocyte proliferation and suppression of inflammation; found in higher concentrations in epidermis than dermis
- Decreases lipid peroxidation and subsequent free radical formation
- Coagulation, inflammation, immune defense, angiogenesis
- Fibrosis/scar formation



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Zinc deficiency

- Maxfield et al 2021: An estimated 17% of global population is deficient; rates higher in S. Asia, sub-Saharan Africa and Central America.
- Briefel et al 2000 using data from NHANES: adequate zinc intake was achieved by ~55% of people. Children ages 1–3, adolescent females ages 12–19, and people ≥71 were at greatest risk of inadequate intake.

Zinc and diabetic foot ulcer

- Momen-Heravi et al 2017: RDBPCT in 60 subjects ages 40 to 85 with grade 3 diabetic foot ulcer, randomized to either 220 mg zinc sulfate (50 mg elemental zinc) or placebo QD x 12 weeks.
- Zinc supplementation resulted in significant reductions in ulcer size; also benefited FBS, serum insulin, HOMA-IR, HbA1c, and QUICKI.
- Subjects taking zinc also had significant improvements in plasma total antioxidant capacity and total glutathione, and significant decreases in hsCRP and plasma malondialdehyde (a marker of lipid peroxidation).

Zinc, C, & Arginine for Pressure Ulcer

- Frías Soriano et al 2004: Open design in 39 people (mean age 74.7 ±12.9 yrs) with grade 3 or 4 pressure ulcers took oral nutritional supplement QD x 3 weeks, containing: arginine 3g, Vit C 250mg, Zinc 9mg
- Following 3 weeks of supplementation, median wound area decreased significantly from 23.6 cm2 to 19.2 cm2 (a reduction of 29%). Median healing of wound area was 0.34 cm2 QD (just over 2 days to heal 1 cm2). Amount of exudate in infected ulcers and incidence of necrotic tissue also decreased significantly.

Zinc, Vit C & E in Children with Burn Wounds

- Barbosa et al 2009: prospective RDBPCT in 32 patients randomized to either supplementation or control.
- Supplementation consisted of vitamin C (1.5x upper intake level), vitamin E (1.35x upper intake level), and zinc (2x RDA) for 7 days starting on day 2 of hospital admission.
- Time to wound healing was significantly shortened in the supplement group (5.3 days vs 7.5 in controls). Malondialdehyde level also significantly dropped in the supplement group.

Bromelain

- A glycoprotein and proteolytic enzyme derived as aqueous extract from the fruit and stem of the pineapple plant.
- Reduces vascular permeability, inhibits formation of prostaglandin E2, acts as fibrinolytic agent.
- Analgesic effects thought to be related to anti-inflammatory activity.

Bromelain- dental studies

- de la Barrera-Núñez et al 2014: RDBPCT in 34 people undergoing 3rd molar extraction (bromelain 150mg QD x 3d then 100mg days 4-7, versus placebo)
  - Found no difference in inflammation level or oral aperture
- Bormann et al 2016: dose-finding study compared 1000 FIP to 3000 FIP & 4500 FIP (equiv to 400mg, 1200mg, & 1800mg). 75 pts randomized to the 3 dose arms. Pts underwent 2 wisdom tooth extraction surgeries- one with bromelain, the other without.
  - Higher doses were not superior/different
  - Trend towards improvement for facial swelling, pain, and analgesic use with highest dose, but did not reach ss

Bromelain- dental studies

- Ghensi et al 2017: 84 pts undergoing impacted third molar surgery randomized to:
  - no drug (control group)
  - Bromelain 40mg Q 6hrs x 6 days postop
  - Dexamethasone submucosal injection 4mg preop
  - Dexamethasone submucosal injection 4mg preop and bromelain 40mg Q 6hrs x 6 days postop
- Postop D7: Group 4 had statistically significant reduction in postop swelling and analgesic use compared to control.

Bromelain- dental studies

- Majid & Al-Mashhadani 2014: RDBPCT in pts undergoing impacted 3rd molar surgery, randomized to bromelain (1000mg), diclofenac (100mg), or placebo, for 1d preop and 4d postop.
  - Both bromelain and diclofenac led to significant reduction in pain compared to placebo; effects on pain, swelling, and trismus were similar with both for all measures at 1, 3, and 7d postop.

Bromelain- dental studies

- Gupta et al 2022: randomized controlled triple-blind trial in 72 pts undergoing impacted 3rd molar surgery, with 5 days of either Bromelain 500mg TID or aceclofenac 100mg BID
  - Bromelain group had a significant decrease in edema and trismus compared to aceclofenac group on postop D2 and D7. Bromelain had similar analgesic efficacy with aceclofenac.

Curcumin

- Anti-inflammatory compound extracted from turmeric root (*Curcuma longa*)
- Effects may include enhancement of granulation tissue formation, collagen deposition, tissue remodeling, wound contraction; reduction of ROS

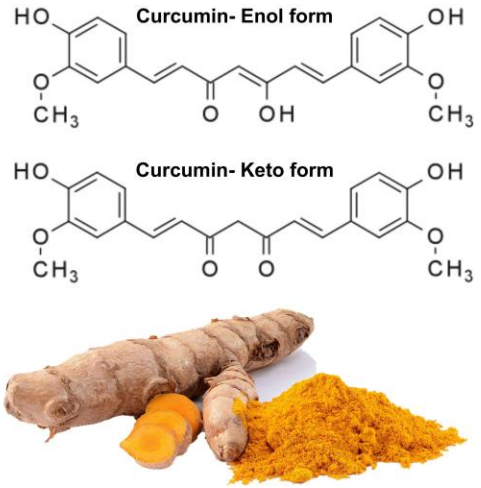

Image: Zheng et al 2016

Curcumin

- Enhances wound healing in experimental models
- Both topical and oral preparations have been utilized
- Due to low bioavailability and high first-pass metabolism, topical app may have more pronounced effects on wound healing compared to oral administration.
- Human data largely pertains to oral mucositis

Curcumin and oral mucositis

- Dharman et al 2021 systematic review and meta-analysis on curcumin for prevention or reduction of oral mucositis in people with H&N cancer receiving radiation or combined radiochemotherapy.
- 9 trials (7 randomized controlled, 2 non-randomized controlled), total N of 582 pts included in analysis
- Trials utilized topical gel, mouthwash, or PO curcumin or turmeric for tx periods up to 8 weeks

Dharman et al continued

- Studies showed delay in onset or decreased incidence of OM with curcumin compared to controls
- Studies also showed reduced severity/grade OM with curcumin
- Prophylactic use of curcumin delayed the onset of OM with RR of 0.38 and reduced the severity of oral mucositis with RR of 0.48

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Questions & Discussion

Thank you for attending today.

luciusk@upmc.edu

412 623 3023